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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	18

DATE MAILED: 01/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/788,280	BURT ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *1-8,14-30 and 35-57* is/are withdrawn from consideration.

5)☒ Claim(s) *13* is/are allowed.

6)☒ Claim(s) *9-12 and 31-34* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election with traverse of Group IV in Paper No. 17 is acknowledged. The traversal is on the ground(s) that that is would not be a serious burden to search the non-elected Groups II, VIII, IX and X. This is not found persuasive because the non-patent literature search required for the groups is diverse. Additionally, a method that will elicit an immune response to an infectious agent, such as viruses will not overlap with methods that are drawn to treating allergies. Because the etiologies and pathologies differ in the diseases of each group the search for one method of preventing a disease will not overlap with the other disease targets.

The requirement is still deemed proper and is therefore made FINAL.

Applicant requests a rejoinder of the product claims with the process claims. Applicant is advised that a rejoinder of claims is possible at a later date if the product is eventually found patentable. Guidance on treatment of product and process claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. §103(b) is set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86.

> To facilitate examination under § 103, where product and process claims are presented in the same application, applicant may be called upon under 35 U.S.C. § 121 to elect claims to either the product or process. The claims to the non-elected invention will be withdrawn from further consideration. However, in the case of an elected product claim, rejoinder will be permitted when a product claim is found allowable and the withdrawn process claim depends from or otherwise includes all the limitations of an allowed product claim. Withdrawn process claims not commensurate in scope with an allowed product claim will not be rejoined. In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104 - 1.106. If the application containing the rejoined claims is not in condition for allowance, the subsequent Office action may be made final, or, if the application was already under final rejection, the next Office action may be an advisory action.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper No. 9 and 12, is attached to the instant Office Action.

Drawings

The drawings have been approved by the draftsperson.

Claim Objections

Claim 13 is objected to because of the following informalities: The claim is dependent on a rejected claim, the claim would be allowable if rewritten in independent form. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9, 31 and 32 rejected under 35 U.S.C. 102(b) as being anticipated by Lowell G.H. (U.S. Pat. No. 5,726,292, IDS Paper No. 9).

The instant invention is drawn to a vaccine composition comprising a proteosome and a viral protein antigen. Specifically, a influenza haemagglutinin (HA) antigen is desired, the HA/ proteosome composition has particles of the median size 150-1000 nm. The HA/ proteosome mixture is 1:1 or 1:4. The composition is passed though a standard 0.2 μm or 0.8 μm filter.

The proteosome of the instant invention were prepared (see specification example 1, page 14) from outer membrane protein of Group B type 2 *Neisseria meningitides* by extraction of phenol-killed bacterial paste with a solution of 6% Empigen BB (EBB) in 1 M calcium chloride followed by precipitation with ethanol, solubilization in 1% EBB-Tris/EDTA-saline and then precipitation with ammoniumsulfate. The precipitates were re-solubilized in the 1% EBB buffer, dialyzed and stored in 0.1% EBB at -70.degree. C. Proteosomes may also be prepared by omitting the ammonium sulfate precipitation step to shorten the process. Portions of stock influenza split product antigens were complexed to and formulated with proteosomes using diafiltration/ultrafiltration methods or by using dialysis. For either method, the influenza split product was dissolved in saline buffered solution containing the desired detergent e.g. Empigen BB (EBB) at 1% or, at 0.1%-2% of EBB or other suitable detergent depending on the type of detergent used and was then mixed with proteosomes in the saline buffered 1% Empigen solution (or other appropriate detergent at appropriate concentrations as described above) at various proteosome:HA (wt/wt) ratios ranging from 1:4, 1:1, 2:1, 4:1 and 8:1. To remove Empigen, the mixture was then subjected to ultrafiltration/diafiltration technology or was exhaustively dialyzed across a dialysis membrane with a 10,000 Molecular Weight cut-off (MWCO) or functionally similar membranes with MWCO ranges of 1,000-30,000 against buffered saline.

Lowell discloses that proteosomes are hydrophobic membranous, multimolecular membrane proteins. They may be obtained from any of a number of different organisms, in this instance from Group B type 2b meningococci. Coupling may be accomplished by dialysis or lyophilization. The cell extracts were obtained by extraction of packed bacterial cells with a solution containing 0.1M sodium acetate pH 5.0, 0.5M CaCl.sub.2 and 3% Empigen BB. Ethanol was added to the mixture to a concentration of 20% v/v and the precipitate removed by centrifugation. The second stage of the proteosome preparation consisted of isolating the outer membrane proteins from the other membrane components by dissolving either of the products from the first stage (i.e. either the vesicles or the direct cell extract) at a concentration of approximately 2 mg protein/ml in a buffer (hereafter referred to as TEEN-1%) containing 0.05 molar trishydrochloride, 0.15M NaCl, 0.01M EDTA and 1% Empigen BB brought to pH 8.0 (see column 5, line 35 to column 6, line 10). The proteosoame protein mixture is complexed via dialysis method (see column 6, line45 to column 7 line 41). The proteosomes, stored in TEEN-1% buffer at a concentration about 1 mg/ml, are added to a TEEN-1% solution of the peptide. Ratios of protein:peptide (weight:weight) that have been used have ranged from 1:1 to 1:40. The proteosomes were added to provide a 1:1 ratio with gp160 (see 17, line 35 to column 18 line 45). The resulting product was dialyzed across a 1000 MWCO spectra Por 6 or 7 membrane for 10 days at 4C against Tris buffered saline changing the buffer daily. Solution was collected from dialysis bag(s). The vaccine was filtered through a 0.22 μm filter the vaccine may need to be pre-filtered through a 0:8 or 0.45 μm m filter or just a 0.45 μm m filter. Therefore, the instant invention is anticipated by Lowell.

Claims 9-11 rejected under 35 U.S.C. 102(b) as being anticipated by Levi et al. (Vaccine, 1995, IDS Paper No. 9).

The instant invention is drawn to a vaccine composition comprising a proteosome and a viral protein antigen. Specifically, a influenza haemagglutinin (HA) antigen is desired, the HA/ proteosome composition has particles of the median size 150-1000 nm. The HA/ proteosome mixture is 1:1 or 1:4. The composition is passed though a standard 0.2 μm or 0.8 μm filter.

The proteosome of the instant invention were prepared (see specification example 1, page 14) from outer membrane protein proteosome of Group B type 2 *Neisseria meningitides* by extraction of phenol-killed bacterial paste with a solution of 6% Empigen BB (EBB) in 1 M calcium chloride followed by precipitation with ethanol, solubilization in 1% EBB-Tris/EDTA-saline and then precipitation with ammoniumsulfate. The precipitates were re-solubilized in the 1% EBB buffer, dialyzed and stored in 0.1% EBB at -70.degree. C. Proteosomes may also be prepared by omitting the ammonium sulfate precipitation step to shorten the process. Portions of stock influenza split product antigens were complexed to and formulated with proteosomes using diafiltration/ultrafiltration methods or by using dialysis. For either method, the influenza split product was dissolved in saline buffered solution containing the desired detergent e.g. Empigen BB (EBB) at 1% or, at 0.1%-2% of EBB or other suitable detergent depending on the type of detergent used and was then mixed with proteosomes in the saline buffered 1% Empigen solution (or other appropriate detergent at appropriate concentrations as described above) at various proteosome:HA (wt/wt) ratios ranging from 1:4, 1:1, 2:1, 4:1 and 8:1. To remove Empigen, the mixture was then subjected to ultrafiltration/diafiltration technology or was exhaustively

dialyzed across a dialysis membrane with a 10,000 Molecular Weight cut-off (MWCO) or functionally similar membranes with MWCO ranges of 1,000-30,000 against buffered saline.

Levi et al. disclose the preparation of outer membrane protein proteosome which were purified from Group B type 2 *Neisseria meningitides* using modifications of previously described (see materials and methods page 1354) methods by extracting phenol-killed bacterial paste with a solution of 6% Empigen BB in 1M calcium chloride followed by removal of debris by using 20% ethanol and then precipitation of outer membrane complex vesicles using 45% ethanol. Proteosomes were isolated from lipopolysaccharide by solubilization using homogenization and sonication in a 1% Empigen, Tris/EDTA/saline buffer and then precipitating with ammonium sulfate three times. Two influenza peptides from the nucleoprotein NP55-69 and NP147-158 and one haemagglutinin protein HA91-1008 were synthesized. The peptides to protesosmes were mixed at a 4:1 ration (weight /weight) in PBS containing 1% Empigen. The mixture was dialyzed across a dialysis membrane with a 1000 dalton cut off. Figure 1 (page 1355) shows the antibody production of the proteosome HA91-108 peptide. Figure 3 (page 1356) shows the protective effect of a multivalent formulation of a proteosome for challenge against influenza.

The mere recitation of newly-discovered function or property, inherently possessed by things in the prior art, does not cause the claim drawn to those things to distinguish over the prior art (See *In re Best, Bolton, and Shaw* 195 USPQ 430 (CCPA 1977), *In re Schreiber* 44 USPQ2d 1429). The instant reference is silent in regards to the size of the proteosome HA particles, however, the proteosomes are prepared using the same methods as those set out in the specification of the instant invention. The specification indicates that diafiltration/ultrafiltration

or dialysis may be used to produce the HA proteosome complex. The vaccine particle disclosed in the reference would inherently have the same size as the particle claimed (claim 11).

Therefore, the instant invention is anticipated by Levi et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-12 and 31-34 are under 35 U.S.C. 103(a) as being unpatentable over Levi et al. (Vaccine, 1995, IDS Paper No. 9) and Lowell G.H. (U.S. Pat. No. 5,726,292, IDS Paper No. 9).

The instant invention is drawn to a vaccine composition comprising a proteosome and a viral protein antigen. Specifically, a influenza haemagglutinin (HA) antigen is desired, the HA/

proteosome composition has particles of the median size 150-1000 nm. The HA/ proteosome mixture is 1:1 or 1:4. The composition is passed though a standard 0.2 μm or 0.8 μm filter.

The proteosome of the instant invention were prepared (see specification example 1, page 14) from outer membrane protein proteosome preparations of Group B type 2 *Neisseria meningitides* by extraction of phenol-killed bacterial paste with a solution of 6% Empigen BB (EBB) in 1 M calcium chloride followed by precipitation with ethanol, solubilization in 1% EBB-Tris/EDTA-saline and then precipitation with ammoniumsulfate. The precipitates were re-solubilized in the 1% EBB buffer, dialyzed and stored in 0.1% EBB at -70.degree. C. Proteosomes may also be prepared by omitting the ammonium sulfate precipitation step to shorten the process. Portions of stock influenza split product antigens were complexed to and formulated with proteosomes using diafiltration/ultrafiltration methods or by using dialysis. For either method, the influenza split product was dissolved in saline buffered solution containing the desired detergent e.g. Empigen BB (EBB) at 1% or, at 0.1%-2% of EBB or other suitable detergent depending on the type of detergent used and was then mixed with proteosomes in the saline buffered 1% Empigen solution (or other appropriate detergent at appropriate concentrations as described above) at various proteosome:HA (wt/wt) ratios ranging from 1:4, 1:1, 2:1, 4:1 and 8:1. To remove Empigen, the mixture was then subjected to ultrafiltration/diafiltration technology or was exhaustively dialyzed across a dialysis membrane with a 10,000 Molecular Weight cut-off (MWCO) or functionally similar membranes with MWCO ranges of 1,000-30,000 against buffered saline.

Levi et al. teaches the preparation of outer membrane protein proteosome which were purified from Group B type 2 *Neisseria meningitides* using modifications of previously described

(see materials and methods page 1354) methods by extracting phenol-killed bacterial paste with a solution of 6% Empigen BB in 1M calcium chloride followed by removal of debris by using 20% ethanol and then precipitation of outer membrane complex vesicles using 45% ethanol. Proteosomes were isolated from lipopolysaccharide by solubilization using homogenization and sonication in a 1% Empigen, Tris/EDTA/saline buffer and then precipitating with ammonium sulfate three times. Two influenza peptides from the nucleoprotein NP55-69 and NP147-158 and one haemagglutinin protein HA91-1008 were synthesized. The peptides to protesosmes were mixed at a 4:1 ration (wight /weight) in PBS containing 1% Empigen. The mixture was dialyzed across a dialysis membrane with a 1000 dalton cut off. Figure 1 (page 1355) shows the antibody production of the proteosome HA91-108 peptide. Figure 3 (page 1356) shows the protective effect of a multivalent formulation of a proteosome for challenge against influenza. The reference is silent in regards to the size of the proteosome/HA particle achieved by their coupling method. The reference does not teach filtering the vaccine before administering it to an animal.

Lowell teaches that proteosomes are hydrophobic membranous, multimolecular membrane proteins. They may be obtained from any of a number of different organisms, in this instance from Group B type 2b meningococci. Coupling may be accomplished by dialysis or lyophilization. The cell extracts were obtained by extraction of packed bacterial cells with a solution containing 0.1M sodium acetate pH 5.0, 0.5M CaCl.sub.2 and 3% Empigen BB. Ethanol was added to the mixture to a concentration of 20% v/v and the precipitate removed by centrifugation. The second stage of the proteosome preparation consisted of isolating the outer membrane proteins from the other membrane components by dissolving either of the products from the first stage (i.e. either the vesicles or the direct cell extract) at a concentration of

approximately 2 mg protein/ml in a buffer (hereafter referred to as TEEN-1%) containing 0.05 molar trishydrochloride, 0.15M NaCl, 0.01M EDTA and 1% Empigen BB brought to pH 8.0 (see column 5, line 35 to column 6, line 10). The proteosoame protein mixture is complexed via dialysis method (see column 6, line45 to column 7 line 41). The proteosomes, stored in TEEN-1% buffer at a concentration about 1 mg/ml, are added to a TEEN-1% solution of the peptide. Ratios of protein:peptide (weight:weight) that have been used have ranged from 1:1 to 1:40. The proteosomes were added to provide a 1:1 ratio with gp160 (see 17, line 35 to column 18 line 45). The resulting product was dialyzed across a 1000 MWCO spectra Por 6 or 7 membrane for 10 days at 4C. against Tris buffered saline changing the buffer daily. Solution was collected from dialysis bag(s). The vaccine was filtered through a 0.22 μm filter the vaccine may need to be pre-filtered through a 0.8 or 0.45 μm m filter or just a 0.45 μm m filter. The reference teaches that the proteosome:peptide concentration can vary (see column 6, lines 47-67), the reference does not teach that the proteosome need to be present at a greater proportion compared to the peptide. The reference does not teach utilizing HA antigen in the preparation of the proteosome composition.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to filter the proteosome vaccine formulation as taught by Lowell before administering the vaccine to an animal. One of ordinary skill in the art would have been motivated to do sterile filter the vaccine in order store the composition for subsequent administration to an animal. Although the reference of Levi et al. is silent in regards to the size of the proteosome/HA particle one of ordinary skill in the art would expect that the particle taught by Levi et al. has the same size as the instantly claimed particle because the method steps in obtaining the particle are the

same as those disclosed in the instant specification. The specification does not indicate that the ultrafiltration/diafiltration produces an unexpected result because the specification clearly indicates that ordinary dialysis could be used to achieve the composition. Optimizing experimental conditions, including the ratio of proteosome to peptide, falls within the skills of an ordinary artisan. Therefore, the instant invention is obvious over Levi et al. and Lowell.

Allowable Subject Matter

The vaccine formulation of claim 13, utilizing a proteosome:HA mixture of 4:1 would be allowable. Figure 1c indicates that this formulation produces a significantly greater immune response a compared to the 1:1 or 1:4 formulation, which is not anticipated by the prior art.

Conclusion

Claims 9-12 and 31-34 are rejected.

Claim 13 is objected to for depending on a rejected claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D. 1/27/03